UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/489,394	01/21/2000	Vanessa Hsei	P1085R6	5782

25213 7590 05/08/2003

HELLER EHRMAN WHITE & MCAULIFFE LLP
275 MIDDLEFIELD ROAD
MENLO PARK, CA 94025-3506

EXAMINER	
HELMS, LARRY RONALD	
ART UNIT	PAPER NUMBER
1642	

DATE MAILED: 05/08/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/489,394	HSEI ET AL.	
	Examiner	Art Unit	
	Larry R. Helms	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *30 January 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *124-132* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *124-132* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *8* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Request for Continued Examination

1. The request filed on 1/30/03 for a Continued Examination (RCE) under 37 CFR 1.114 based on parent Application No. 09/489,394 is acceptable and a RCE has been established. Claims 124-132 are pending and are currently under prosecution. An action on the RCE follows.

2. NOTE: newly added claims 38-46 have been renumbered as 124-132 respectively under Rule 1.126. Claim 125 (filed as claim 39) has been changed to depend from claim 124 (Claim 39 was depended on claim 39 as filed in the amendment of 1/30/03).

3. Claims 1-7, 9-11, 13, 15-16, 18-24, and 26-37 have been cancelled.

4. The text of those sections of Title 35 U.S.C. code not included in this office action can be found in a prior Office Action.

5. The following Office Action contains some NEW GROUNDS of rejection.

Claim Objections

6. Claim 132 is objected to because of the following informalities: The claim has a typographical error in the term "DC20" which should be "CD20". Appropriate correction is required.

Rejections Withdrawn

7. The rejection of claim 1-7, 9-11, 13, 15-16, 18-24, 26-37 under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention is withdrawn in view of the amendments to the claims.

The following are some NEW GROUNDS of rejections

Claim Rejections - 35 USC § 112

8. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

9. Claim 126 and 127 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 126 and 127 are indefinite for reciting "Fab", "Fv", "scFv" because the exact meaning of the terms is not clear in the context of claim 124 which recites "free sulfhydryl group of a cysteine residue within the hinge region". It is not clear how a Fab, FV or scFv can have a cysteine residue from a hinge region of an antibody when as evidenced from Cruse et al (Illustrated Dictionary of Immunology, CRC Press, page 107, 1995) that the Fab and Fd don not have a hinge cysteine. Likewise a scFv would not have a hinge. Does the claim mean a cysteine is engineered into the molecule or is

an entire hinge region that adds a cysteine added to the molecule? In addition, it is art known that a hinge regions does not only contain a cysteine (or more cysteines) but other amino acids are required for the definition of the hinge.

Double Patenting

10. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

11. Claims 124-132 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1, 20, 25, 26, 28, 31, 32-36 of copending Application No. 09/726,258 in view of Carter et al (Antibody Engineering, A practical approach, IRL Press, chapter 13, pages 291-308, 1996, IDS #8) and Allan et al (U.S. Patent 5,620,689, filed 6/95).

The claims in the instant application are directed to conjugates of an antibody fragment directed to HER2 or CD20 wherein the conjugate has one or two PEG molecules of 20 or 30 kD conjugated to a free cysteine wherein the apparent molecular weight is 500, 800, 1800. The claims in the 09/726,258 application are similar in scope

and directed to an IL-8 antibody fragment and carriers, and labeled conjugates. It would have been obvious to substitute antibodies that bind HER2 and CD20 for those in the 09/726,258 application in view of Carter et al and Allan et al who teach the therapeutic benefits of the antibodies. Carter et al teach a conjugate of PEG to an anti-HER2 antibody (see pages 301-303) and Allan et al teach an anti-CD20 antibody conjugated to PEG (see column 2, lines 64-66).

This is a provisional obviousness-type double patenting rejection.

12. Claims 124-132 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1 and 27 of copending Application No. 09/355,014 in view of Carter et al (Antibody Engineering, A practical approach, IRL Press, chapter 13, pages 291-308, 1996, IDS #8) and Allan et al (U.S. Patent 5,620,689, filed 6/95).

The claims in the instant application are directed to conjugates of an antibody fragment directed to HER2 or CD20 wherein the conjugate has one or two PEG molecules of 20 or 30 kD conjugated to a free cysteine wherein the apparent molecular weight is 500, 800, 1800. The claims in the 09/355,014 application are similar in scope and directed to an IL-8 antibody fragment. It would have been obvious to substitute antibodies that bind HER2 and CD20 for those in the 09/726,258 application in view of Carter et al and Allan et al who teach the therapeutic benefits of the antibodies. Carter et al teach a conjugate of PEG to an anti-HER2 antibody (see pages 301-303) and Allan et al teach an anti-CD20 antibody conjugated to PEG (see column 2, lines 64-66).

This is a provisional obviousness-type double patenting rejection.

Claims 124-132 are directed to an invention not patentably distinct from claims 1 and 27 of commonly assigned 09/355014. Specifically, see above.

The U.S. Patent and Trademark Office normally will not institute an interference between applications or a patent and an application of common ownership (see MPEP § 2302). Commonly assigned 09/355014, discussed above, would form the basis for a rejection of the noted claims under 35 U.S.C. 103(a) if the commonly assigned case qualifies as prior art under 35 U.S.C. 102(f) or (g) and the conflicting inventions were not commonly owned at the time the invention in this application was made. In order for the examiner to resolve this issue, the assignee is required under 37 CFR 1.78(c) and 35 U.S.C. 132 to either show that the conflicting inventions were commonly owned at the time the invention in this application was made or to name the prior inventor of the conflicting subject matter. Failure to comply with this requirement will result in a holding of abandonment of the application.

A showing that the inventions were commonly owned at the time the invention in this application was made will preclude a rejection under 35 U.S.C. 103(a) based upon the commonly assigned case as a reference under 35 U.S.C. 102(f) or (g), or 35 U.S.C. 102(e) for applications filed on or after November 29, 1999.

Claim Rejections - 35 USC § 103

13. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

14. Claims 124-130 are rejected under 35 U.S.C. 103(a) as being unpatentable over Gonzalez et al (U.S.Patent 6,133,426, priority to 1/22/98) and further in view of Zapata et al (FASEB J. 9:A1476, 1995, IDS #8).

The claims are summarized as conjugates of an antibody fragment directed to CD18 wherein the conjugate has one or two PEG molecules of 20 or 30 kD conjugated to a free cysteine wherein the apparent molecular weight is 500, 800, 1800.

Gonzales et al. teach a conjugate comprising an antibody Fab' (Fab'-SH) covalently attached to a single PEG molecule, wherein the PEG has an average molecular weight of at least about 20kD, 30 kD (see especially example T at columns 120-123) Gonzales et al. also teach that the conjugate of an antibody Fab' fragment and a single PEG is a conjugate that has an apparent size of at least about 500, 800, 1800 KD (see Figure 60 for the 20 kD conjugate) and the PEG is taught to be attached at the free Cys of the hinge region (see e.g., column 120 at lines 15-37). Gonzalez et al does not teach an ani-CD18 antibody. This deficiency is made up for in the teachings of Zapata et al.

Zapata et al. teach a conjugate consisting essentially of a humanized anti-CD18 Fab' fragment covalently coupled via a sulfhydral group in the hinge region to a single chain PEG molecule (MePEG) that is either 5 kD or 10kD (see entire Abstract). Zapata et al. also teach that the Fab' fragment coupled to either size PEG did not interfere with the ability of the antibody to bind CD18, and reduced the clearance rate relative to the native Fab' molecule (Abstract middle). Zapata et al. note that the ability to extend the clearance rate of an antibody Fab' fragment without affecting antigen binding increased significantly the potential therapeutic value of the antibody (concluding remark). Zapata et al. also note that although both the 5 kD and 10 kD forms of PEG reduced serum clearance, the 10 kD form of PEG was better than the 5 kD form (see last third of Abstract). Consequently, Zapata et al. clearly recognized that increasing the size of the PEG resulted in a further reduction the clearance rate. Thus the teaching of Zapata et

al. establish that the size of the PEG molecule was a variable that affected the desirable property of reducing serum clearance rates, with a larger size producing a better effect.

It would have been prima facie obvious to one of ordinary skill in the art at the time the claimed invention was made to have used the anti-CD18 antibody of Zapata for the antibody of Gonzalez et al.

One of ordinary skill in the art would have been motivated to and had a reasonable expectation of success to have used the anti-CD18 antibody of Zapata for the antibody of Gonzalez et al because Gonzalez et al teach the antibodies modified with PEG can be used for therapy. In addition, one of ordinary skill in the art would have been motivated to and had a reasonable expectation of success to have used the anti-CD18 antibody of Zapata for the antibody of Gonzalez et al because the antibody of Zapata et al is also conjugated to PEG and it has use a s a therapeutic agent.

Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references.

15. Claims 124-130 are rejected under 35 U.S.C. 103(a) as being unpatentable over Faanes et al (U.S. Patent 5,695,760, filed 4/24/95, IDS #8) and further in view of Zapata et al (FASEB J. 9:A1476, 1995, IDS #8) and Braxton (US Pat. No. 5,766,897, IDS #8).

The claims have been described supra.

Faanes et al teach the methods and modifications of antibodies with attachment of PEG molecules to the antigen binding fragments. Faanes et al teach the anti-CD18 antibody (see column 7, lines 50-55) and humanization (column 14, line 40), fragments

of the antibody (Fab and F(ab')2) (see column 10, lines 12-13), derivatives of PEG (column 12, lines 19-28), antibodies with biological excipient (column 19, lines 49-57) which are sterile (column 20, line 20), and the antibodies can be modified to contain about 2-15 molecules of PEG (column 6, lines 21-24) with PEG 5 kD to higher molecular weight PEGs (column 14, lines 9-10) . Faanes et al also teach a method for separating fragments of antibodies from PEG-modified fragments (column 13-14) The method can separate PEG-modified antibody fragments with 1, 2, 3, etc, PEG molecules (column 18, lines 19-34). Faanes et al also teach the determination of the apparent molecular weight of the conjugates using the Stokes radius (column 19, lines 35-41) and teaches an antibody which was modified with PEG has a molecular weight of 540 kD (column 19, lines 35-41). Faanes et al does not teach attachment of PEG to the hinge region of the antibody fragment or that the PEG is specifically 20 kD. These deficiencies are made up for in the teachings of Zapata et al and Braxton.

Zapata et al teach covalent attachment of MePEG to an antibody fragment of Fab' or F(ab')2 that binds a therapeutically relevant antigen of CD18 through the single free thiol in the hinge region.

Braxton teach methods for the PEGylation of proteins by attaching a PEG molecule via the thiol group on a free cysteine (see entire document, e.g., column 12 especially lines 48-50). Braxton teach that the molecular weight of the attached PEG may be from 200 to 20,000 MW (i.e., from about 0.2 to 20 kD) and that particularly for relatively small proteins that generally have short half lives and because of their small

size have fewer PEG sites available, the PEG moiety used should be of a higher molecular weight (see especially lines 48-65).

It would have been prima facie obvious to one of ordinary skill in the art at the time the claimed invention was made to have produced a conjugate comprising an antigen binding fragment of CD18 with PEG attached in the hinge region as taught by Zapata et al and producing a conjugate with the claimed characteristics as taught by Faanes et al in view of the teachings of Braxton.

One of ordinary skill in the art would have been motivated to and had a reasonable expectation of success to have produced a conjugate comprising an antigen binding fragment with PEG attached in the hinge region as taught by Zapata et al and producing a conjugate with the claimed characteristics as taught by Faanes et al using a high molecular weight PEG as taught by Braxton because Zapata et al teach the "humanized anti-CD18 Fab' fragment, which contains a single free thiol, was expressed in E. Coli and recovered in high yield". In addition, Zapata et al teach "modification of the anti-CD18 Fab' with either size of MePEG maleimide did not alter the ability of this molecule to bind antigen". In addition, Zapata et al teach that the pharmacokinetic data show that the MePEG-Fab' species had reduced clearance as compared to the native Fab' and because Zapata et al teach MePEG was used to selectively modify the single free thiol of the Fab' polypeptide in a rapid and efficient reaction.". In addition, one of ordinary skill in the art would have been motivated to and had a reasonable expectation of success to have produced a conjugate comprising an antigen binding fragment with PEG attached in the hinge region as taught by Zapata et al and producing a conjugate

with the claimed characteristics as taught by Faanes et al with a high molecular weight PEG as taught by Braxton because Faanes et al clearly teaches mPEG of up to 40 kD may alternatively be employed (see column 12, lines 61-63) and in view of Zapata et al's teaching that a higher molecular weight (as admitted by applicants) led to extended serum half life, therefore it would be obvious to use a higher MW PEG and as such in view of Faanes et al which teaches 40Kd one skiil in the art would use a higher MW to get reduced clearance and as such this would increase the apparent MW of the conjugate. In addition, Braxton teach methods for the PEGylation of proteins by attaching a PEG molecule via the thiol group on a free cysteine (see entire document, e.g., column 12 especially lines 48-50) and Braxton teach that the molecular weight of the attached PEG may be from 200 to 20,000 MW (i.e., from about 0.2 to 20 kD) and that particularly for relatively small proteins that generally have short half lives and because of their small size have fewer PEG sites available, the PEG moiety used should be of a higher molecular weight (see especially lines 48-65). Therefore, it would be obvious to go to higher molecular weight PEG of 20 or 30kD because of th eteachings of Braxton and Zapata et al.

Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references.

16. Claims 124-132 are rejected under 35 U.S.C. 103(a) as being unpatentable over Faanes et al (U.S. Patent 5,695,760, filed 4/24/95, IDS #8) in view of Zapata et al

(FASEB J. 9:A1476, 1995, IDS #8) and Braxton (US Pat. No. 5,766,897, IDS #8) as applied to claims 124-130 above and further in view of Carter et al (Antibody Engineering, A practical approach, IRL Press, chapter 13, pages 291-308, 1996, IDS #8) and Allan et al (U.S. Patent 5,620,689, filed 6/95).

Claims 124-130 have been described supra. Claims 131-13 recite wherein the antigen binding site is for HER2 and CD20.

Faanes et al has been described supra. Faanes et al does not teach an antibody to HER2 or CD20. These deficiencies are made up for in the teachings of Carter et al and Allan et al.

Carter et al teach a conjugate of PEG to an anti-HER2 antibody (see pages 301-303)

Allan et al teach an anti-CD20 antibody conjugated to PEG (see column 2, lines 64-66).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to have created the claimed invention by substituting the antibody that binds HER2 and an antibody that binds CD20 for the anti-CD18 Fab' conjugate taught by Faanes in view of Zapata et al and Braxton.

One of ordinary skill in the art would have been motivated to add PEG to an anti-HER2 and anti-CD20 Fab' fragment using the method of Faanes in view of Zapata et al. and Braxton because Carter et al. teach the usefulness of an anti-HER2 monoclonal antibody Fab' fragments in treatment and diagnosis of cancer and because both Zapata et al. and Braxton teach that addition of PEG reduces serum clearance of therapeutics

and reduces immunogenicity. Given the availability of the anti-HER2 and anti-CD20 Fab' fragment and the methods of adding PEG, including a 20kD single chain PEG to an antibody Fab' fragment, the ordinary artisan at the time the invention was made would have had a reasonable expectation of producing the instant invention. Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

17. Claims 124-132 are rejected under 35 U.S.C. 103(a) as being unpatentable over Koumenis et al (Protein Science 7(suppl.1):73 7/1998) and further in view of Carter et al (Antibody Engineering, A practical approach, IRL Press, chapter 13, pages 291-308, 1996, IDS #8) and Allan et al (U.S. Patent 5,620,689, filed 6/95).

The claims have been described supra.

Koumenis et al teach a Fab' modified with PEG of molecular weight of 20 and 30 kD and the hydrodynamic volumes were from 300kda to 2millian kDa and the molecules had no loss of bioactivity and the study demonstrated the importance of using higher MW PEG at fewer sites. Koumenis et al does not teach an anti-HER2 or anti-CD20 antibody modified with PEG. These deficiencies are made up for in the teachings of Carter et al and Allan et al.

Carter et al teach a conjugate of PEG to an anti-HER2 antibody (see pages 301-303)

Allan et al teach an anti-CD20 antibody conjugated to PEG (see column 2, lines 64-66).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to have created the claimed invention by substituting the antibody that binds HER2 and an antibody that binds CD20 for the anti-CD18 Fab' conjugate taught by Koumenis et al.

One of ordinary skill in the art would have been motivated to add PEG to an anti-HER2 and anti-CD20 Fab' fragment using the method of Koumenis et al because Carter et al teach the usefulness of an anti-HER2 monoclonal antibody Fab' fragments in treatment and diagnosis of cancer and because Koumenis et al teach that addition of PEG reduces serum clearance of therapeutics. Given the availability of the anti-HER2 and anti-CD20 Fab' fragment and the methods of adding PEG, including a 20kD single chain PEG to an antibody Fab' fragment, the ordinary artisan at the time the invention was made would have had a reasonable expectation of producing the instant invention. Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

Conclusions

18. No Claims are allowed.

19. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Larry R. Helms, Ph.D, whose telephone number is (703) 306-5879. The examiner can normally be reached on Monday through Friday from 7:00 am to 4:30 pm, with alternate Fridays off. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa, can be reached on (703) 308-3995. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

20. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 308-4242.

Respectfully,

Larry R. Helms Ph.D.

703-306-5879